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Review Article

Sex Differences in Drug Disposition

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Physiological, hormonal, and genetic differences between males and females affect the prevalence, incidence, and severity of diseases and responses to therapy. Understanding these differences is important for designing safe and effective treatments. This paper summarizes sex differences that impact drug disposition and includes a general comparison of clinical pharmacology as it applies to men and women.

1. Introduction

At the core of personalized medicine is the identification of factors influencing disease processes and therapy [1, 2]. Consequently, characterizing the pharmacokinetics and pharmacodynamics of a drug in diverse populations is essential in improving therapeutic effectiveness while minimizing adverse events [3]. For a drug to work, it is necessary to reach and maintain a minimum drug concentration at the site(s) of action. Exceeding the effective concentration will increase risk of adverse events. Accordingly, drug concentrations must be maintained within a defined therapeutic range.

Many factors influence circulating drug concentrations, as well as the concentrations at the sites of action, and determine the resulting outcome [4]. Sex, in particular, can influence how the body handles a drug as well as what the drug does to the body. This paper, which examines sex differences in pharmacokinetics and pharmacodynamics, is an update of current knowledge on this topic and includes peer-reviewed literature published until October 2010 [5]. The keywords used were: *sex/gender differences, pharmacokinetics, pharmacodynamics, adverse drug events, and sex differences in drug metabolism/elimination.* All reviewed manuscripts pertain to publications concerning humans only, written and published in the English language.

1.1. Gender Differences versus Sex Differences. Gender, a social construct, is expressed in terms of masculinity and femininity. It is defined by the way people perceive themselves and how they expect others to behave. Gender is largely determined by culture. Sex differences result from the classification of organisms based on genetic composition as well as reproductive organs and function [6]. Men and women differ in response to drug treatment and occupational exposures, a consequence of differences in body weight, height, body surface area, total body water, and the amount of extracellular and intracellular water. Pharmacokinetics and pharmacodynamics are also attributable to the differences seen between males and females [5, 7–9].

1.2. General Background. Since pharmacokinetics, pharmacodynamics, and responses during clinical trials differ between men and women, U.S. FDA regulations and guidance are in place to ensure that both sexes are represented in all phases of clinical trials and that medical products are

labeled to alert physicians and patients to sex differences in drug responses. In 1999, the National Institutes of Health published the "Agenda for Research on Women's Health for the 21st Century," concluding that sex-related differences in pharmacokinetics and pharmacodynamics must be further assessed.

In an effort to overcome gaps in knowledge regarding the actions of drugs in women, more women are now included in clinical trials. The NIH Biennial Report of the Director of 2006-2007 reported that in 2006, of 624 extramural and intramural phase III clinical research protocols (499,430 participants), 63% were women [10, 11]. More attention is currently being drawn towards the ways in which clinical therapeutics can be tailored according to sex, age, body weight, and genotype to yield the best possible outcomes [12].

2. Sex Differences in Adverse Events

The FDA Adverse Events Reporting System (AERS) is a voluntary database of adverse events. Based on an analysis of AERS data and other data resources, women experience more adverse events than men, and in general, these adverse events are of a more serious nature [13–17]. The U.S. General Accounting Office (GAO) reviewed the ten drugs withdrawn from the market during the period January 1, 1997 through December 2000; eight of the ten were withdrawn due to greater risks of adverse effects in women [18].

Sex-related differences in the frequencies of adverse events reporting may be due to pharmacokinetic or pharmacodynamic factors, polypharmacy, or differences in reporting patterns [19] (Table 1). Women are generally smaller and have a different body composition than men, the recommended dose may result in higher drug concentrations or area under the concentration time curve (AUC) in women because the drug has lower clearance and/or smaller volume of distribution (V_d) [20]. Alternatively, pharmacodynamic factors (alterations in drug-target numbers or responses) may increase female sensitivity to specific drugs [21]. In this instance, free drug concentrations and drug persistence would be similar in men and women, but women would respond to a greater or lesser extent. It is also possible that sex differences between men and women result in similar rates of adverse events but that women experience more severe events. Another plausible explanation might be attributed to prescribing patterns; women ingest more medications than men, increasing the risk of adverse events from drug-drug interactions.

3. Sex Differences in Pharmacokinetics

3.1. Drug Absorption and Bioavailability. Drug absorption and bioavailability are influenced by drug- and route-specific factors (oral, dermal, rectal, vaginal, intramuscular, intravenous, intra-arterial, intrathecal, and intraperitoneal). Routes of absorption occur across body surfaces, such as the gastrointestinal tract, respiratory tract, or skin, which differ in males and females. For example, drug absorption occurs at different sites throughout the gastrointestinal tract, and rate of absorption is influenced by gut transit times, lipid solubility of the agent, pH at the site of absorption, and the ionization and molecular weight of the agent [5]. Transit times differ significantly in men and women, with mean transit times being shorter in men (44.8 hours) than in women (91.7 hours) [22]. While fiber ingestion decreases transit time, female gut transit times are consistently longer [22]. Sex differences have also been noted in bile acid composition, which may impact the solubility of various drugs. Men have higher concentrations of cholic acid, while women have higher concentrations of chenodeoxycholic acid [23].

The FDA evaluated sex differences in bioequivalence among 26 studies submitted to the agency between 1977 and 1995 [20, 24]. It is a major concern that over a 20-year period, only 26 studies submitted to the FDA had data addressing sex differences in drug absorption. Among the 26 studies, there were 47 datasets addressing sex differences in maximum concentration (Cmax) and AUC. None of the datasets had more than 20 individuals of each sex. Most had no more than 10 men or women, so the sample size available to assess sex differences in bioavailability was limited. However, among these studies, the Cmax was greater in women 87% of the time and AUC was greater in women 71% of the time.

Other investigators have utilized multidrug cocktails to assess bioavailability and metabolism across age and sex [25]. The advantage of this approach is the ability to phenotype multiple cytochrome P450 (CYP) enzymes including CYP1A2, 2C19, 2D6, 2E1, and 3A4 (although differences in intestinal and hepatic metabolism and transport may complicate the interpretation of the data). Using this approach, the investigators suggested that the activities of CYPs 2C19, 2D6, and 3A4 were equivalent and that the activities of CYPs 1A2 and 2E1 were decreased in women than in men. However, using well-characterized human liver samples, another group of investigators observed ~2-fold greater hepatic CYP3A4 activity in women, suggesting sex differences in first pass metabolism and bioavailability [26]. Analysis of 24 studies of CYP3A4 substrates observed that clearance was greater in women than men for 15 substrates (60%) [27]. These divergent data suggest that sex differences in absorption and bioavailability remain unresolved.

In addition to sex differences in bioavailability, it is important to consider that food interactions (e.g., grapefruit juice), gut motility and transit time, gut pH, biliary secretion and gut flora, enterohepatic circulation and oral contraceptives can differentially influence the bioavailability of a drug in men and women [28, 29]. For example, it was recently observed that polyethylene glycol enhances the bioavailability of ranitidine in men and decreases it in women [30]. Sex differences in bioavailability of Cyclosporine A have also been observed after a fat-rich meal: decreased bioavailability in females and increased bioavailability in males [31]. It has been hypothesized that, because of differences in subcutaneous lipid content, the bioavailability of transdermally administered drugs is different in women [32]. Additionally, women have greater respiratory minute ventilation and lower tidal volume, which may result in decreased ingestion of

Table 1: Suggested reasons for sex differences in adverse event reporting.

Reason for sex difference	Pharmacological reason	Pharmacological factors
Women are overdosed	Pharmacokinetics	Sex differences in volume of distribution Sex differences in protein binding of drugs Sex differences in transport, phase 1, and phase 2 metabolism
Women are more sensitive	Pharmacodynamics	Sex differences in drug targets (i) receptor number (ii) receptor binding (iii) signal transduction following receptor binding
Women are prescribed multiple medications	Drug-drug interactions	Drug-drug induced alterations Pharmacokinetics Pharmacodynamics

(Table modified from Soldin and Mattison [5]).

inhaled aerosol drugs, such as ribavirin and cyclosporine, although only limited data are available so far [23, 33].

3.1.1. Gastric and Hepatic Enzymes. An important part of bioavailability includes the gastric and hepatic enzymes and transport proteins that oral drugs interact with prior to reaching the systemic circulation [34, 35]. Gastric and hepatic enzymes and transporters change across the course of development, forming the basis for sex differences [36]. These metabolic and transport processes are critical for the success or failure of drugs developed for oral use [35]. Successful oral drugs are soluble, permeable, and poorly metabolized by intestinal and hepatic enzymes. For example, the bioavailability of alcohol is greater in women than in men, with Cmax and AUC being greater. These can be partly ascribed to differences in V_d and gastric alcohol dehydrogenase activity [37].

3.1.2. Transport Proteins. Transport proteins play a critical role in transporting drugs into and out of all cells and are consequently involved in hepatobiliary and urinary excretion [34]. Tissue distribution and elimination pathways, as well as efficacy and toxicity of drugs, are explained in many cases by transport proteins. One interesting example is paclitaxel neurotoxicity, which appears to be dependent on phenotypic and genotypic variation in CYP3A4/5, as well as transport proteins (OATP 1B1/3 and PGP), which vary with sex [38]. Variability in the intestinal expression of transport proteins may result in sex differences in plasma drug concentrations. For example, p-glycoprotein (PGP), a membrane adenosine triphosphatase transporter protein found in high concentrations in the enterocytes of the small intestine, is encoded by the multidrug resistance transporter-1 gene (MDR1) expressed in the human intestine, liver and other tissues [39]. PGP, expressed in higher numbers in men, has been shown to decrease intracellular concentrations of certain drugs at the intestine by transporting them out of the enterocytes and back into the intestinal lumen. This mechanism results in the drug being repeatedly exposed to intestinal drug-metabolizing enzymes [23, 40]. Synthetic and endogenous sex hormones have been shown to regulate PGP expression and inhibit PGP function at the gut wall, enhancing drug absorption [41]. Absorptive transporters such as H+/ditripeptide transporter and organic anion transporting polypeptide (OATP) facilitate drug absorption, while efflux transporters such as PGP sometimes work as drug absorption barriers [42].

Sex differences are also exhibited by the serotonin 5-HT_{1A} receptor and serotonin transporter (5-HTT), which is a target for selective serotonin reuptake inhibitors (SSRIs), psychotropic drugs used in the treatment of depression, anxiety, and personality disorders. Women have significantly higher 5-HT_{1A} receptor and lower 5-HTT binding potentials throughout the cortical and subcortical brain regions and exhibit a positive correlation between 5-HT_{1A} receptor and 5-HTT binding potentials for the hippocampus. Thus, sex differences in 5-HT_{1A} receptor and 5-HTT binding potentials may result in biological distinctions in the serotonin system, thereby contributing to sex differences in the prevalence of psychiatric disorders such as depression and anxiety [43].

3.1.3. Enterohepatic and Renal Handling of Drugs or Metabolites. Gastric fluids are generally more acidic in males than females (pH 1.92 versus pH 2.59), and basal and maximal flow of gastric fluid and acid secretion are both higher in men [44]. Reduced pH results in decreased absorption of weak acids and increased absorption of weak bases. The absorption of antidepressants, the majority of which are weak bases, is greatly increased in women, further enhanced by slower rates of gastric emptying and prolonged gut transit times [45].

The kidneys are responsible for the maintenance of water/electrolyte balance, the synthesis, metabolism, and secretion of hormones, and excretion of waste products from metabolism as well as most drugs and xenobiotics. The human kidney demonstrates sex-related differences in the subunits of glutathione-S-transferase isoenzyme [46].

Iron also has significant differences between males and females in gastrointestinal absorption. In preadolescent males and females, it has been shown that 45% of ingested iron is incorporated into erythrocytes by females compared to 35% in males (iron-regulated surface determinant −0.78) [47, 48].

3.2. Distribution. Once absorbed and in the circulation, most drugs bind to plasma proteins. Distribution is a function of multiple physiologic and body composition characteristics. Sex differences in these parameters may account for differences in the concentration of a drug at the target site and result in varying responses. However, differences in protein binding between men and women are generally rare, and there is still no convincing link between protein-binding differences and sex-specific ADRs, with the exception of lignocaine and diazepam [48]. On average, total body water, extracellular water, intracellular water, total blood volume, plasma volume, and red blood cell volume are greater for men. Therefore, if an average man and an average woman are exposed to the same dose of a water-soluble drug, V_d will be increased in the man, thus decreasing drug concentration.

For lipid-soluble drugs, there is generally an increased V_d in females. Alcohol, a water-soluble drug, has a smaller V_d in women than in men, producing higher Cmax in women [49]. The V_d values of salbutamol (albuterol) and ofloxacin have been shown to be significantly greater in men, most likely due to sex differences in lean body mass [50]. The liver accounts for a greater percentage of lean body mass in women compared to men. It is currently believed that the larger liver mass and smaller V_d observed in women accounts for the more rapid rate of elimination of alcohol from the blood [51].

Sex differences in blood distribution and regional blood flow can also impact pharmacokinetics. In general, the reference values for resting blood flow to organs and tissues for 35-year-old males and females show significant differences as a percentage of cardiac output. For example, blood flow to skeletal muscle is greater for men and to adipose tissue is greater for women. These differences may reflect sexbased differences in the percentage of total body mass represented by each tissue [52]. Blood distribution will also impact clearance rates. Females exhibit decreased liver blood flow rates which, despite higher CYP3A4 amounts and activity, may result in lower drug clearance [45].

The main binding proteins for various drugs in plasma are albumin, α_1-acid glycoprotein (AAG), and α globulins. AAG levels and AAG glycosylations vary in association with endogenous and exogenous estrogen, inducing hepatic glycosylation of these proteins and thus decreasing plasma AAG levels. Albumin concentrations do not consistently vary by sex [53]. Estrogens also increase the levels of the serum-binding globulins (sex-hormone-binding globulin, corticosteroid-binding globulin, and thyroxin-binding globulin) [54]. Sex-related differences in plasma binding of selected compounds are listed in Table 2. Variations in levels of plasma binding can alter the free (active) fraction of drugs.

Therapeutic drug monitoring is the measurement of specific drugs in order to maintain a relatively constant circulating drug concentration. Drugs that are monitored tend to have a narrow "therapeutic range"—the drug quantity required to be effective is not far removed from the quantity that causes significant side effects and/or signs of toxicity. Maintaining drug concentrations within the therapeutic range is not as simple as giving a standard dose of medication. Often, if the free fraction increases, there is a shift of the drug to the tissues/target or resultant higher clearance, with the total concentration not changing, for example, phenytoin.

Table 2: Sex differences in plasma binding.

Compound	Description
Testosterone	Plasma protein binding: F > M, Estrogen increases
Chlordiazepoxide	Plasma protein binding: M > F > F_{oc}
Diazepam	Free fraction: F_{oc} (1.99%) > F (1.67%) > M (1.46%)
Lidocaine	Free fraction: F (34%), M (32%) < F_{oc} (37%)
Warfarin	Free fraction: F > M
Morphine, Phenytoin Oxazepam, Lorazepam	No differences

oc: oral contraceptives.
Table modified from Soldin and Mattison [5].

3.2.1. Body Composition. Body fat as a percentage of total body weight is higher in women than in men and increases by age in both sexes [55]. The total body fat values are 13.5 kg in an adult reference male and 16.5 kg for an adult reference female [56]. The larger proportions of body fat in women may increase the body burden of lipidsoluble, slowly metabolized toxicants. Differences in body fat and in organ blood flow in women have been implicated in the faster onset of action and prolonged duration of neuromuscular blockade in women (e.g., vecuronium and rocuronium) [57, 58]. Differences in body fat content and in protein binding are responsible for sex-related pharmacokinetic differences in the distribution of diazepam (free fraction: in females 1.67% versus 1.46% in males). Females have been shown to have larger V_d than males (V_d = 1.87 versus 1.34 L/kg) [59].

Several studies have observed that when dose is corrected by body weight, some of the sex differences seen in pharmacokinetics disappear [20]. This suggests body weight (and by inference, composition) may be responsible for some differences seen in drug disposition. A recent study examined the plasma concentrations of the antibiotic clindamycin in twenty-four male and female subjects. Higher plasma concentrations were seen in women. However, when the 600 mg dose was normalized to individual body weight, plasma concentrations between men and women were comparable [60]. Aliskirin, an antihypertensive rennin inhibitor, as well as fluconazole, an antifungal drug, both appear to require dosage adjustments by body weight [61, 62]. Furthermore, the pharmacokinetics of citalopram does not display differences between males and females when adjusted by dose and body weight [63].

3.2.2. Cardiac Output. Cardiac output and regional distribution of flow are important for drug disposition. Cardiac output is commonly standardized and reported as the cardiac index, which is similar for both sexes between 18 and 44 years

of age. The distribution of cardiac output, or regional blood flow, is similar for men and women for some organs (adrenal 0.3%, bone 5%, brain 12%, lung 2.5%, skin 5%, and thyroid 1.5%, reported as percent of cardiac output) and different for others (adipose: male = 5%, female = 8.5%; heart: male = 4%, female = 5%; kidney: male = 19%, female = 17%; liver: male = 25%, female = 27%; muscle: male = 17%, female = 12%), reflecting sex-based differences in body composition [64].

3.3. Drug Metabolism. Drug metabolism (biotransformation) occurs predominantly in the liver, as well as in extrahepatic sites such as the intestinal tract, lung, kidney, and skin. Hepatocytes and intestinal cells express significant levels of CYP3A and phase II enzymes such as uridine diphosphate glucoronosyltransferase (UGT), which may significantly contribute to the first pass metabolism of many orally administered drugs (see discussion above on bioavailability). Lipid solubility, protein binding, the dose, and the route of exposure all affect the rate of biotransformation.

Despite the large variations in drug metabolism among individuals, correction for height, weight, surface area, and body composition eliminates some but not all of the "sex-dependent" differences. However, sex-dependent differences in biotransformation have been observed for drugs such as nicotine, chlordiazepoxide, flurazepam, aspirin (acetylsalicylic acid), and heparin [65–69].

3.3.1. Cytochrome P450 (CYP) Group. The main enzymes involved in drug metabolism belong to the CYPs. These are a large family of related enzymes housed in the smooth endoplasmic reticulum of the cell. While the CYP enzymes discussed in this paper are all coded for by autosomal chromosomes, it is possible that sex-related disparities in pharmacokinetics arise from variations in the regulation of the expression and activity of CYP enzymes through endogenous hormonal influences. For reviews that deal specifically with CYP enzymes, please refer to [23, 70–76].

3.3.2. Hepatic and Extrahepatic Metabolism. Ingested compounds may remain unchanged (and possibly accumulate in a storage compartment) or, based on their degree of lipophilicity and polarity, they may be subject to metabolism. Hepatic drug metabolism is divided into two usually sequential enzymatic reactions: phase I and phase II reactions. Some of the CYP enzymes show clear sex-related differences (Table 3). In general, lipophilic compounds have a tendency to pass through biological membranes and/or be stored and are often susceptible to phase I types of metabolism [77].

Sex-related differences have been shown for some CYPs, with a higher activity in females for CYP3A4 (Table 3) [78]. An analysis of previously published studies of 14 different drugs demonstrated that females displayed an average of 20–30% increased clearance for drugs that were CYP3A substrates compared to those of males [27]. In 2009, Lutz and colleagues demonstrated for the first time in a Caucasian population that the endogenous marker for CYP3A activity—the metabolic ratio of 6 β-hydroxycortisol to cortisol found in urine—was significantly increased in females compared to males [79].

By studying the activity of sex hormones, as a consequence of physiological, pathological, or pharmacological manipulations, researchers now believe that many of the changes seen in CYP enzymes may be gender specific [36]. The sex-dependent expression of CYP3A4 is thought to be regulated by sex-specific temporal patterns of plasma growth hormone release by the pituitary gland. Males display a pulsatile pattern while females exhibit a more continuous pattern of release. Growth hormone regulation of CYP3A4 has been discerned in primary human hepatocyte cultures; CYP3A4 protein and mRNA are induced by continuous treatment with growth hormone and suppressed with pulsatile treatment [80]. CYP3A4 activity, however, has not been seen to vary throughout the menstrual cycle, suggesting that sex hormones may not be responsible for the gender-specific expression observed [23].

Antihistamines, in particular, have been shown to exhibit sex-specific differences in pharmacokinetics. They act as CYP2D6 substrates, which have been shown to exhibit slower metabolic elimination in women. This may explain why women are more vulnerable to sedation and drowsiness effects of antihistamines than men. Gender differences in PGP expression in the brain may also underlie the sedative side effects often experienced by women [23].

However, even if there are true sex differences in drug pharmacokinetics, only few drugs exhibit significantly different plasma concentrations in women. A comprehensive review of second-generation (atypical) antipsychotics concludes that even though sex differences in cases of adverse events have not been well studied, some adverse effects such as weight gain, hyperprolactinemia, and cardiac effects, are particularly problematic for women [81]. Most studies that were reviewed indicate that clozapine and olanzapine are associated with greater body weight gain than other atypical antipsychotics and that serious adverse effects such as metabolic syndrome (which includes increased visceral adiposity, hyperglycemia, hypertension and dyslipidemia induced by atypical antipsychotics) are more frequent in females. Although women are at a lower risk of sudden cardiac death, they have a higher risk of induced long-QT syndrome from antiarrhythmic and, probably, antipsychotic drugs [82, 83]. This adverse effect has been seen with drugs that block cardiac voltage-gated potassium channels, prolonging repolarization and the QT interval [23].

Metabolism of chemicals may be estimated by basal metabolic rates. For all ages, on average, men have a higher basal metabolic rate than women. Since the metabolism of adipose tissue differs from that of muscle tissue, some of the differences between men and women are attributable to body composition metabolism of adipose tissue [84]. A lower basal metabolic rate per unit body surface area reflects the lower lean body mass in women due to a smaller skeletal muscle component [85].

Hepatic clearance of drugs is a function of liver blood flow and hepatic enzyme activity. Although cardiac output and hepatic blood flow are lower in women than in men

Table 3: Sex differences in hepatic clearance by route of metabolism/elimination.

Phase I Enzymes			
Metabolic route	Model substrates	Drugs metabolized by route	Sex-specific activity
CYP1A	Caffeine, nicotine paracetamol (acetaminophen)	Clomipramine, clozapine, olanzapine, paracetamol, tacrine, theophylline	M > F [65]
CYP2C9	Dapsone, (*S*)-mephenytoin	Ibuprofen, (*S*)-warfarin, tolbutamide, fluvastatin, glipizide, losartan, irbesartan, piroxicam, tolbutamide, phenytoin, fluvastatin, nelfinavir	M = F [66]
CYP2C19	(*S*)-Mephenytoin Diazepam	Lansoprazole, omeprazole, hexobarbital, mephobarbital, citalopram, celecoxib, irbesartan, imipramine, piroxicam, propranolol (in part)	M = F [67]
CYP2D6	Dextromethorphan, debrisoquine, sparteine	Codeine, encainide, flecainide, fluoxetine, hydrocodone, metoprolol, paroxetine, mexilitine, phenformin, propranolol, sertraline, timolol, haloperidol, clomipramine, desipramine, imipramine, propafenone, testosterone	M < F [68]
CYP2E1	Chlorzoxazone	—	M > F [69]
CYP3A	Midazolam, dapsone, cortisol, Lidocaine, nifedipine, erythromycin	Alprazolam, alfentanil, astemizole, atorvastatin, carbamazepine, cisapride, clarithromycin, cyclosporin, cyclophosphamide, diazepam,diltiazem, erythromycin, estradiol, fentanyl, indinavir, itraconazole, ketoconazole, lovastatin, quinidine, nimodipine, nisoldipine, quinidine, ritonavir, verapamil, tacrolimus, simvastatin, vincristine, vinblastine, tamoxifen, tirilazad, troglitazone	F > M [70]
Phase II enzymes			
Metabolic route	Model substrates	Drugs metabolized by route	Sex-specific activity
UDP-glucuronosyl-transferases	Caffeine	Clofibric acid, diflusinal, ibuprofen, mycophenolate, mofetil, paracetamol, zidovudine	M = F [68, 71]
Sulfotransferases	Caffeine	—	M > F [72]
N-Acetyl-transferases	Caffeine, dapsone	Catecholamine derivatives, mercaptopurine, isoniazid, hydralazine	M = F [73]
Methyl-transferases	Norepinehrine, epinephrine	Azathioprine, dopamine, levodopa, 6-mercaptopurine, thioguanine, tazathioprine	M > F [74]

Table modified from Soldin and Mattison [5].

normalized per m^2/kg, sex differences in hepatic enzymes also play a major role in determining sex-related pharmacokinetic activity. At the canalicular surface of hepatocytes, PGP will direct the biliary excretion of certain drugs, and its expression has been found to be twofold lower in women than in men. Consequently, women display increased and sustained intracellular concentrations of PGP substrates, increased activity of hepatic drug-metabolizing enzymes, and thus increased clearance of the drug [23]. Much is unknown regarding PGP expression although it is currently thought to be controlled and regulated by sex hormones.

3.4. Drug Elimination. Two processes, metabolism and elimination, are responsible either separately or together for drug inactivation. Without these means, drugs would continuously circulate throughout our bodies, bind to various receptors, and interrupt important physiological processes. Drugs are generally eliminated from the body by renal, hepatic, or pulmonary routes. Consequently, drugs may be eliminated from the body in sweat, tears, breast milk, and expired air. The most common routes are via feces and urine.

The kidney is the major organ of drug excretion of either the parent drug compounds or drug metabolites. There are known sex differences in all three major renal functions-glomerular filtration, tubular secretion and tubular reabsorption. Renal clearance is generally higher in men [86, 87]. A recent study on the transdermal absorption of fentanyl, a pain management drug for cancer patients, found that particularly at high doses, urinary excretion of fentanyl was markedly decreased in women. Gender also has a significant impact on the elimination of the loop diuretic torasemide, contributing to higher rates of adverse drug reactions in women. Hospitalizations due to ADRs from diuretics are more prevalent in women, irrespective of differences in prescription rates between the sexes [88]. Adjusting for age, body mass index (BMI), and modification of diet in renal disease (MDRD), oral clearance of torasemide

was on average one-third lower in women, associated with 30%–40% higher mean AUC_{24} and C_{max} values in females than in males [88].

Renal function is important for elimination. Chemicals can be excreted into the urine through glomerular filtration, passive diffusion, and active secretion. Increases in renal blood flow and glomerular filtration increase the elimination rate of drugs cleared by the kidneys. When standardized for body surface area, renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption are all greater in men than in women [89, 90].

3.5. Anesthesia and Opioids. Sex-dependent differences among the three primary opioid receptor subtypes—mu, delta, and kappa—have been extensively studied. The kappa opioid receptor subtype may be sex-dependently modulated by *Mc1r*, a gene that encodes for melanocortin-1 receptors. Women with two or more variant alleles of this gene were more responsive to pentazocine than women with one or no variants of the gene. This antinociceptive phenomenon was not seen in men [91]. Morphine, a mu-opioid receptor agonist, has been shown to be more potent and also exhibits a slower onset and offset in women [92]. Additionally, women perceived more pain and required greater dosages of morphine to achieve the same antinociceptive effect as men [93]. This may be explained by the higher mu-opioid receptor binding in various cortical and subcortical brain regions exhibited in women than in men. According to a 2009 comprehensive review on sex-specific influences on pain, women appear to be not only more sensitive to pain but also more vulnerable to chronic, widespread, and postprocedural pain conditions [94]. Designing and tailoring treatment plans for pain may certainly need to take sex into account.

3.6. Self-Administered Drugs. Sex differences in pharmacokinetics of self administered drugs and in drug dependence have also been explored. Biologically, it is believed that sex and gonadal hormones underlie many of the differences seen in drug sensitivity, addictive behavior, and susceptibility to drug abuse. In general, women appear to be more vulnerable to the rewarding and dependent properties of cannabinoids, alcohol, opioids, and cocaine. Many animal models of gender influences on substance abuse have confirmed clinical findings [95]. With an ever-growing population using self-administered drugs and the pressing need to effectively address and treat substance abuse, larger clinical studies focusing on this topic must be carried out.

4. Sex Differences in Pharmacodynamics

For cortisol and first-generation antihistamines, there appears to be significant sex differences in pharmacodynamics. Because women are more sensitive to cortisol suppression, they may also be more sensitive to the effects on basophils and helper T lymphocytes [96–98]. This is interesting because of the balance in sex differences in both pharmacokinetics and pharmacodynamics, suggesting that men and women should receive the same dose and treatment schedule. A recent epidemiological study showed that women being treated for allergic diseases display lowered levels of eosinophils and IgE than men [23]. Additionally, there appear to be a lower expression of ERK/MAPK signaling genes, leukocyte extravasation, antigen presentation, and chemokine signaling in women than in men [23]. Sex differences in pharmacodynamics may also affect cardiovascular medications. Digoxin therapy has been shown to differ by sex and was associated with an increase in all-cause death among women [99].

5. Sex-Specific Conditions That Impact Pharmacokinetics and Pharmacodynamics

5.1. Influence of Sex Hormones. There are numerous examples supporting the contention that female sex hormones impact drug-metabolizing pathways. For example, drug-induced long QT syndrome has a higher rate of incidence in females, particularly during the ovulatory phase of the menstrual cycle compared to the luteal phase [100]. It has been established that there exists a basal sex hormonal regulatory impact on cardiac potassium channels and that in drug-induced QT prolongation, drug-hormone interactions seen at particular doses cause a blockade in these channels [101–103]. Heightened sensitivity to opioids in females has been consistently observed. We now know that opioid receptor density and dopaminergic function is influenced by female hormones, leading to a higher rate of ADRs in women under anesthesia [104], such as difficulties in respiration and increased chronic pain. Moreover, sex hormones have also been implicated in functional altering of GABA receptors, the target of anesthetic drugs [105].

Estrogen has membrane, cytosolic, and nuclear targets [106]. Estrogen has been shown to bind and modulate membrane ion channels and receptors, such as cardiac ATP-K+ cardiac channels and opioid receptors. The estrogen receptor is a cytosolic target which serves to trigger downstream kinase activation [107]. Nuclear targets include hormone receptors such as ERα, which directly modulates CYP1B1 expression [108]. A recent review on sex differences in pharmacokinetics of antidepressants highlights possible hormone-drug competition for hepatic metabolic enzymes. Since estrogen is a substrate for CYP3A4 and CYP1A2, antidepressant metabolism may be significantly impacted during the late luteal phase of the menstrual cycle or with estrogen replacement therapy [45].

5.2. Changes in Sex Hormone Levels. Increased levels of estrogen and progesterone alter hepatic enzyme activity, which can increase drug accumulation or decrease elimination of some drugs. Female steroid hormones and prolactin play a role in autoimmunity. Regulation of immunity and interactions between the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes contribute to the 2- to 10-fold incidence and severity of autoimmune/inflammatory diseases in females compared to males. Most autoimmune diseases are detected in females of

Table 4: Some drugs that display sex differences in pharmacokinetics.*

Drug	Pharmacokinetic parameter	Comments
Acebutolol [76]	Area under the concentration-time curve	The concentration-time profile is larger in women, suggesting greater therapeutic and potential side effects
Aspirin [36]	Clearance, half-life	Aspirin is cleared more rapidly from women
Benzylamine		Following transdermal absorption, women excrete 3 times more than men
Beta-Blockers; Atenolol [77]	Oral clearance lower in women, lower volume of distribution in women resulting in higher systemic exposure	The greater reduction in blood pressure in women was due to pharmacokinetic and not pharmacodynamic differences
Cefotaxime [79]	Clearance	Clearance is decreased in women
Ciprofloxacin [80]	Clearance	Clearance is lower in women
Cephradine [81]		Slower rate of absorption and lower bioavailability in the female; increased clearance and decreased terminal elimination half-life in pregnancy
Clozapine [82]		significantly higher plasma levels for women
Diazepam [83]	Plasma binding	Larger volume of distribution in women
Ethanol [86]	Volume of distribution, clearance, and first-pass metabolism	When ethanol is ingested, men metabolize more in first pass metabolism; in addition the volume of distribution is smaller in women
Ferrous Sulfate	Absorption	Absorption higher in prepubertal girls than boys
Fluoroquinolones [87]	Volume of distribution	Lower in women
Gemcitabine [79]	Clearance	Clearance is lower in women
Heparin [79]	Clearance	Clearance is lower in women
Iron [79]	Absorption measured as % of the dose incorporated into red blood cells	More ingested iron is absorbed by women than men
Methylprednisolone [90]	Plasma binding, clearance, volume of distribution, and half-life	Plasma binding and V_d are similar in men and women; CL is increased in women and as a consequence, half-life is shorter
Metronidazole	Volume of distribution	Smaller volume of distribution and increased clearance resulting in lower AUC in women
Metoprolol [100]	Plasma binding, clearance, volume of distribution, half-life	Clearance increases during pregnancy, but is smaller in women; V_d smaller in women than men, but increases during pregnancy; plasma binding is unaffected by sex or pregnancy
Midazolam [101]	Considered to be probe for CYP3A4, not substrate for PGP	No sex difference in clearance following either oral or intramuscular administration; interpretation complicated by *differences in intestinal and hepatic CYP3A4 levels*
Mizolastin [102]	Oral availability	Longer duration for absorption in men, contributing to variability in drug concentrations in men and women
Naratriptan [79]	Oral availability, peak concentration	Oral bioavailability being greater in women results in peak concentration is higher in women than men
Ofloxacin	Clearance	Clearance is lower in women
Olanzapine [103]	Higher activity in women for CYP3A4 and CYP2D6	Significantly higher plasma levels for women
Ondansetron [79]	Oral availability, clearance	Oral availability is increased in women
Phenytoin [104]	Plasma binding	*Plasma binding decreases during pregnancy;* however, the intrinsic clearance is unchanged so the free concentration is unchanged

Table 4: Continued.

Drug	Pharmacokinetic parameter	Comments
Prednisolone [105]	Distribution	Oral clearance and volume of distribution significantly higher in men
Propranolol [106]	Plasma binding, clearance, volume of distribution, and half-life	Plasma binding is similar among men and women; however, plasma binding increases during pregnancy. Clearance is smaller in women. V_d is similar in both men and women and does not appear to be altered during pregnancy. Half-life is decreased in women compared to men but does not appear to be altered during pregnancy
Quinine [79]	Plasma binding, clearance, volume of distribution, and half-life	Plasma binding is unaltered during pregnancy, as is clearance. V_d decreases during pregnancy, as does half-life
Rifampicin [9]	Women absorb the drug more efficiently	—
Rizatriptan [79]	Urinary excretion, clearance, volume of distribution, half-life	Urinary excretion is similar in men and women; clearance is greater in men
Rocuronium	Distribution	Prolonged drug duration due to higher fat content and lower organ blood flow in women
Salicylate [108]	Absorption	Increased rates of absorption in women
Selective Serotonin Reuptake Inhibitors [91]	Plasma concentrations are higher in women	Decreased metabolism by hepatic CYP
Vecuronium	Distribution	Prolonged drug duration due to higher fat content and lower organ blood flow in women
Verapamil; Calcium channel blocker [94, 95]	Clearance following intravenous administration more rapid in women, but oral clearance higher in men than women. Substrate for both CYP3A4 and PGP	Sex differences in hepatic and gut CYP3A4 and PGP lead to complex differences in clearance between men and women. Bioavailability from the gut is greater in women. The greater bioavailability leads to increased systemic exposure in women
	Oral clearance is lower in women	

* Pregnancy-related PK changes are in *italics* font.
Table modified from Soldin and Mattison [5].

childbearing age. Metabolic changes can also depend on hormone levels that change during the menstrual cycle, with use of oral contraceptives, throughout pregnancy, or during menopause. For example, some asthmatic women have worsening symptoms before or during menstruation [109]. An increase in oxidative stress in females has been described during intensive physical exercise, particularly in postmenopausal women [110]. Moreover, sex hormone levels throughout the menstrual cycle are associated with the activation of specific hepatic enzymes and the rate of clearance of certain drugs. Caffeine and theophylline clearance, for example, is higher during the early follicular phase and prolonged during the mid-luteal phase [39].

Although sex hormones are thought to play a dominant role in modulating sex-based differences in pharmacokinetics, studies examining this have yielded conflicting results. Midazolam clearance (reflecting CYP3A4 metabolic activity) failed to show fluctuations during the menstrual cycle [111]. Similarly, studies of eletriptan (to treat migraines) demonstrated no sex-related or menstrual cycle-related differences [112].

5.3. Menopause. There are conflicting data that exist on pharmacokinetic changes in women relating to menopausal status. To examine menopause-related alterations in intestinal or hepatic CYP3A4 activity, several studies compared the pharmacokinetics of midazolam, erythromycin, and prednisolone clearance in pre- and postmenopausal women and found no significant differences in drug metabolism according to menopausal status [113].

5.4. Use of Data in Pharmacokinetics. Data acquired on sex differences in absorption, distribution, metabolism and elimination allow exploration of sex differences in disposition and response to chemicals and drugs. Results from clinical trials focusing on HIV-infected female subjects have suggested that there are clinically relevant sex-related differences in the efficacy and safety of drug treatment (Table 4) [114].

6. Conclusions

Males and females may differ in specific drug pharmacokinetics and pharmacodynamics. It is, therefore, essential to understand those sex differences in drug disposition and response, as they may affect drug safety and effectiveness. To minimize therapeutic adverse events, clinicians and the pharmaceutical industry must establish clear therapeutic goals for the drugs of choice prior to treatment of women. It must be determined if the treatment should be assessed by clinical signs and symptoms or by laboratory test results whether drug toxicity will be evaluated by clinical or laboratory assessment, and what determines the appropriate duration of treatment. Furthermore, clinicians should be aware of and understand the principles of clinical pharmacology and absorption, disposition, metabolism, and elimination as they apply to the drug of choice. In particular, the prescribing physician should understand the relationship between drug dose, drug concentration and desired biological effect at the action site, the mechanism of action of the drug, the impact of the chosen drug on the patient's signs, symptoms of adverse effects, and laboratory testing.

In general, data on sex differences are mostly obtained by *post hoc* analysis; therefore, the conclusions that can be drawn are limited. For a better understanding of the basic mechanisms of sex differences, future large-scale prospective studies should be designed with a primary focus on this topic. Although we have been able to articulate many of the sex differences in drug absorption, metabolism, and elimination, it is still necessary to identify the specific ADRs these differences can lead to as well as the mechanisms behind differences seen in pharmacokinetics and pharmacodynamics between the sexes. In particular, the potential for competitive hormone-drug interactions could provide us with more detailed mechanisms behind the pharmacokinetic differences seen between sexes. Further genetic studies in the context of drug toxicity and ADRs would contribute to our understanding of gender-specific pharmacokinetics. More specific data will help to determine the extent to which these differences will have implications for clinical management.

Abbreviations

AAG: Alpha-1 acid glycoprotein
ADR: Adverse Drug Reactions
AERS: Adverse Events Reporting System
ABC: ATP-binding cassette
ADME: Absorption, distribution, metabolism, and excretion
BMR: Basal metabolic rates
CO: Cardiac output
CYP3A: Cytochrome P450-3A
ER: Elimination rate
FDA: Food and Drug Administration
GAO: General Accounting Office
GFR: Glomerular filtration rate
GST: Glutathione-S-transferase isoenzyme
HPA: Hypothalamic-pituitary-adrenal
HPG: Hypothalamic-pituitary-gonadal
IOM: Institute of Medicine
MDR1: Multidrug resistance transporter-1
NIH: National Institutes of Health
OATP: Organic anion transporting polypeptide
PEPT1: H+/ditripeptide transporter
PGP: p-glycoprotein
SGAs: Second-generation (atypical) antipsychotics
SSRI: Selective serotonin reuptake inhibitors
UGT: Uridine diphosphate glucoronosyl transferase.

Conflict of Interests

The authors declare no conflict of interests.

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